CLAIMS

1. An isolated nucleic acid molecule comprising a polynucleotide having a sequence encoding a peptide or polypeptide comprising at least an amino acid sequence set forth in SEQ ID NO:13, or a variant thereof, wherein said peptide or polypeptide specifically binds to at least a portion of an Inhibitor of Apoptosis Protein (IAP).

2. The isolated nucleic acid molecule of claim 1, wherein said portion is at least one BIR domain.

3. The isolated nucleic acid molecule of claim 2, wherein said BIR domain is BIR3.

4. The isolated nucleic acid molecule of claim 1, wherein said specific binding is to a full-length IAP.

5. The isolated nucleic acid molecule of claim 1, wherein said amino acid sequence is selected from the group consisting of the first four amino acid residues of each of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10.

6. An isolated nucleic acid molecule consisting essentially of a polynucleotide having a sequence encoding a peptide or polypeptide comprising at least an N-terminus amino acid sequence set forth in SEQ ID NO:11.

7. An isolated nucleic acid molecule consisting essentially of a polynucleotide having a sequence encoding a peptide or polypeptide comprising at least an N-terminus amino acid sequence of Ala-Val-Pro-Tyr, as set forth in SEQ ID NO:15.

8. An isolated nucleic acid molecule consisting essentially of a polynucleotide having a sequence encoding a peptide or polypeptide comprising at least an N-terminus amino acid sequence set forth in SEQ ID NO:12.

9. An isolated nucleic acid molecule comprising a polynucleotide having a sequence encoding a peptide or polypeptide comprising a first portion of a procaspase-9 that specifically binds at least a portion of an IAP and a second portion of a procaspase-9 containing a mutated active site, wherein said peptide or polypeptide specifically binds at least a portion of an IAP and lacks cysteine protease activity.

10. An isolated nucleic acid molecule comprising a polynucleotide having a sequence encoding a peptide or polypeptide comprising an amino acid sequence of SEQ ID NO:13, and further comprising at least a portion of a caspase-3, wherein said peptide or polypeptide exhibits caspase-3 enzymatic activity that is inhibited by an IAP or an IAP BIR3 domain.

11. The isolated nucleic acid molecule of claim 10, wherein the peptide or polypeptide consists essentially of a caspase-3 in which the amino acid residues corresponding to the amino-terminal two residues of the p12 subunit are substituted with Ala-Val.

12. The isolated nucleic acid molecule of claim 10, wherein the peptide or polypeptide consists essentially of a caspase-3 in which the amino acid residues corresponding to the amino-terminal four residues of the p12 subunit are substituted with residues set forth in SEQ ID NO:13.

13. An isolated nucleic acid molecule comprising a polynucleotide having a sequence encoding a peptide or polypeptide comprising at least a portion of a mutated procaspase-9, wherein said portion fails to undergo normal processing and said portion possesses wild type caspase-9 enzymatic activity.

14. The nucleic acid molecule of claim 13 wherein said portion of a mutated caspase-9 corresponds to SEQ ID NO:1 with an amino acid substitution, deletion, or addition.

15. The nucleic acid molecule of claim 13 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residue 315 substituted by Ala.

16. The nucleic acid molecule of claim 13 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 315 and 330 substituted by Ala.

17. The nucleic acid molecule of claim 13 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 306, 315, and 330 substituted by Ala.

18. The nucleic acid molecule of claim 13 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 316 through 330 deleted.

19. An expression vector comprising a nucleic acid molecule selected from the group consisting of claims 1 – 9 and 13 – 18, operatively linked to regulatory elements.

20. The expression vector of claim 19, wherein the regulatory elements include an inducible promoter.

21. A host cell containing the expression vector of claim 19.

22. The host cell of claim 21, wherein the cell is selected from the group consisting of a bacterium, a yeast, an animal cell, and a plant cell.

23. A peptide or polypeptide comprising at least an amino acid sequence set forth in SEQ ID NO:13, wherein said peptide or polypeptide specifically binds to at least a portion of an Inhibitor of Apoptosis Protein (IAP).

24. The peptide or polypeptide of claim 23, wherein said portion is at least one BIR domain.

25. The peptide or polypeptide of claim 23, wherein said BIR domain is BIR3.

26. The peptide or polypeptide of claim 23, wherein said specific binding is to a full-length IAP.

27. The peptide or polypeptide of claim 23, wherein said amino acid sequence is selected from the group consisting of the first four amino acid residues of each of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10.

28. A peptide or polypeptide comprising the amino acid residues set forth in SEQ ID NO:11 or a variant thereof, wherein said peptide or polypeptide specifically binds to at least a portion of an IAP.

29. A peptide or polypeptide comprising the amino acid residues set forth in SEQ ID NO:15 or a variant thereof, wherein said peptide or polypeptide specifically binds to at least a portion of an IAP.

30. A peptide or polypeptide comprising the amino acid residues set forth in SEQ ID NO:12 or a variant thereof, wherein said peptide or polypeptide specifically binds to at least a portion of an IAP.

31. A peptide or polypeptide comprising a first portion of a procaspase-9, or a variant thereof, that specifically binds at least a portion of an IAP and a second portion of a procaspase-9, or a variant thereof, containing a mutated active site, wherein said peptide or polypeptide specifically binds to at least a portion of an IAP and lacks cysteine protease activity.

32. A peptide or polypeptide comprising an amino acid sequence of SEQ ID NO:13, and further comprising at least a portion of a caspase-3, or a variant thereof, wherein said peptide or polypeptide exhibits caspase-3 enzymatic activity that is inhibited by an IAP BIR3 domain.

33. The peptide or polypeptide of claim 32 comprising a caspase-3, or a variant thereof, in which the amino acid residues corresponding to the amino-terminal two residues of the p12 subunit are substituted with Ala-Val.

34. The peptide or polypeptide of claim 32 comprising a caspase-3, or a variant thereof, in which the amino acid residues corresponding to the amino-terminal four residues of the p12 subunit are substituted with any four contiguous residues set forth in SEQ ID NO:13.

35. A peptide or polypeptide comprising at least a portion of a mutated procaspase-9 or a variant thereof, wherein said portion fails to undergo normal processing and said portion possesses wild type caspase-9 enzymatic activity.

36. The peptide or polypeptide of claim 35 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residue 315 substituted by Ala.

37. The peptide or polypeptide of claim 35 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 315 and 330 substituted by Ala's.

38. The peptide or polypeptide of claim 35 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 306, 315, and 330 substituted by Ala's.

39. The peptide or polypeptide of claim 35 wherein said portion of mutated procaspase-9 corresponds to SEQ ID NO:1 with amino acid residues 316 through 330 deleted.

40. An antibody that specifically binds to a peptide or polypeptide set forth in SEQ ID NO:13 that specifically binds to at least a portion of an IAP.

41. The antibody of claim 40, wherein said antibody inhibits the binding of said peptide or polypeptide to said portion of an IAP.

42. An antibody that specifically binds to an epitope located on the N-terminus of a caspase-9-p12.

43. The antibody of claim 42, wherein said antibody inhibits the binding of a caspase-9-p12 to at least a portion of an IAP.

44. The antibody of claim 41 or 43, wherein said portion is at least one BIR domain.

45. The antibody of claim 44, wherein said BIR domain is BIR1.

46. The antibody of claim 44, wherein said BIR domain is BIR2.

47. The antibody of claim 44, wherein said BIR domain is BIR3.

48. The antibody of claim 42, wherein said antibody inhibits the binding to a full-length IAP.

49. A method for inducing apoptosis in a cell comprising contacting the cell with at least one component selected from the group consisting of:

(a) a peptide or polypeptide of claims 23 – 31 and 35 – 39;

(b) a nucleic acid molecule of claims 1 – 9 and 13 – 18; and

(c) an antibody of claims 40 and 42,

under conditions and for a time sufficient to permit the induction of apoptosis in the cell.

50. The method of claim 49, wherein said peptide or polypeptide is capable of inhibiting caspase-9-p12 binding to at least a portion of an IAP.

51. The method of claim 50, wherein said portion is at least one BIR domain.

52. The method of claim 51, wherein said BIR domain is BIR3.

53. The method of claim 52, wherein said BIR domain is BIR1 or BIR2.

54. The method of claim 50, wherein said peptide or polypeptide inhibits binding to a full length IAP.

55. The method of claim 49, wherein said polypeptide is a procaspase-9 mutant that fails to undergo normal processing.

56. The method of claim 49, wherein said cell overexpresses a peptide or polypeptide capable of inhibiting IAP binding to caspase-9.

57. The method of claim 49, wherein said cell overexpresses a procaspase-9 mutant that fails to undergo normal processing.

58. A method of stimulating apoptosis in a neoplastic or tumor cell, comprising contacting the cell with at least one component selected from the group consisting of:

(a) a peptide or polypeptide of claims 23 – 31 and 35 - 39 and

(b) a nucleic acid molecule of claims 1 – 9 and 13 - 18; and

(c) an antibody of claims 40 and 42,

under conditions and for a time sufficient to permit the induction of apoptosis in the cell.

59. The method of claim 58, wherein said peptide or polypeptide is capable of inhibiting caspase-9-p12 binding to at least a portion of an IAP.

60. The method of claim 58, wherein said peptide or polypeptide is a procaspase-9 mutant that fails to undergo normal processing.

61. The method of claim 58, wherein said cell overexpresses a peptide of polypeptide capable of inhibiting caspase-9-p12 binding to at least a portion of an IAP.

62. The method of claim 58, wherein said cell overexpresses a procaspase-9 mutant that fails to undergo normal processing.

63. The method of claim 58, wherein said cell overexpresses an inhibitor of a caspase.

64. The method of claim 63, wherein the inhibitor inhibits activation or activity of caspase–9.

65. The method of claim 63, wherein the inhibitor is at least a portion of an Inhibitor of Apoptosis protein.

66. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a peptide or polypeptide comprising at least an amino acid sequence set forth in SEQ ID NO:13 that is capable of specifically binding to at least a portion of an IAP with a candidate inhibitor or candidate enhancer; and

(b) detecting cell viability,

wherein an increase in cell viability as compared to a control indicates the presence of an inhibitor and a decrease in cell viability as compared to a control indicates the presence of an enhancer.

67. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a polypeptide selected from the group consisting of the polypeptides of claims 35 - 39; and

(b) detecting cell viability,

wherein an increase in cell viability as compared to a control indicates the presence of an inhibitor and a decrease in cell viability as compared to a control indicates the presence of an enhancer.

68. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a peptide or polypeptide comprising at least an amino acid sequence corresponding to SEQ ID NO:13 that is capable of specifically binding to at least a portion of an IAP with a candidate inhibitor or candidate enhancer; and

(b) detecting the presence of large and small caspase subunits, and therefrom determining the level of caspase processing activity,

wherein a decrease in processing as compared to a control indicates the presence of an inhibitor and an increase in processing indicates the presence of an enhancer.

69. The method of claim 68, wherein the caspase detected is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

70. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a polypeptide selected from the group consisting of the polypeptides of claims 35 - 39; and

(b) detecting the presence of large and small caspase subunits, and therefrom determining the level of caspase processing activity,

wherein a decrease in processing as compared to a control indicates the presence of an inhibitor and an increase in processing indicates the presence of an enhancer.

71. The method of claim 70, wherein the caspase detected is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

72. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a peptide or polypeptide comprising at least an amino acid sequence corresponding to SEQ ID NO:13 that is capable of specifically binding to at least a portion of an IAP with a candidate inhibitor or candidate enhancer; and

(b) detecting caspase enzymatic activity,

wherein a decrease in enzymatic activity as compared to a control indicates the presence of an inhibitor and an increase in enzymatic activity indicates the presence of an enhancer.

73. The method of claim 72, wherein the caspase enzymatic activity detected is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

74. The method of claim 72, wherein the caspase enzymatic activity detected is a presence of a substrate cleavage product produced by a caspase cleavage of a substrate.

75. The method of claim 65, wherein said substrate is acetyl DEVD-aminomethyl coumarin.

76. A method of identifying an inhibitor or enhancer of a caspase-mediated apoptosis comprising:

(a) contacting a cell containing a vector expressing a polypeptide selected from the group consisting of the polypeptides of claims 35 - 39 with a candidate inhibitor or enhancer; and

(b) detecting caspase enzymatic activity,

wherein a decrease in enzymatic activity as compared to a control indicates the presence of an inhibitor and an increase in enzymatic activity indicates the presence of an enhancer.

77. The method of claim 76, wherein the caspase enzymatic activity detected is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

78. The method of claim 76, wherein the caspase enzymatic activity detected is a presence of a substrate cleavage product produced by a caspase cleavage of a substrate.

79. The method of claim 78, wherein said substrate is acetyl DEVD-aminomethyl coumarin.

80. A method for identifying a compound that inhibits a peptide or polypeptide comprising an amino acid sequence set forth in SEQ ID NO:13 that specifically binds at least a portion of an IAP from binding to said portion of an IAP, comprising:

(a) contacting a candidate compound with said peptide or polypeptide in the presence of said portion of an IAP; and

(b) detecting displacement or inhibition of binding of said portion of an IAP from said peptide or polypeptide.

81. The method of claim 80, wherein said portion of an IAP is a BIR3 domain.

82. The method of claim 80, wherein said portion of an IAP is a full length IAP.

83. A method for identifying a compound that inhibits a peptide or polypeptide comprising an amino acid sequence set forth in SEQ ID NO:13 that specifically binds at least a portion of an IAP from binding to said portion of an IAP, comprising:

(a) contacting a candidate compound with said peptide or polypeptide in the presence of said portion of an IAP; and

(b) performing a functional assay that confirms displacement of said portion of an IAP from said peptide or polypeptide.

84. The method of claim 83, wherein the functional assay detects the presence of large and small caspase subunits, and therefrom determining the level of caspase processing activity, wherein a decrease in processing confirms displacement.

85. The method of claim 84, wherein the caspase detected is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

86. The method of claim 83, wherein the functional assay detects the presence of a substrate cleavage product produced by a caspase cleavage of a substrate.

87. The method of claim 86, wherein said substrate is acetyl DEVD-aminomethyl coumarin.

88. A composition comprising a nucleic acid molecule selected from the group consisting of claims 1 – 9 and 13 - 18, and a physiologically acceptable carrier.

89. A composition comprising the expression vector of claim 19, and a physiologically acceptable carrier.

90. A composition comprising a peptide selected from the group consisting of claims 23 – 31 and 35 - 39, and a physiologically acceptable carrier.

91. A composition comprising an antibody of claim 40 or 42, and a physiologically acceptable carrier.

92. A composition comprising an inhibitor or enhancer of apoptosis identified by a method selected from the group consisting of claims 57 – 59, 61, 63, 67, and 71.

93. A method of producing a compound for inhibiting or enhancing apoptosis in a cell, comprising:

(a) identifying an inhibitor or enhancer of apoptosis according to a method selected from the group consisting of claims 66-68, 70, 72, 76, and 80; and

(b) purifying said inhibitor or enhancer.

94. A process for the manufacture of a compound for inhibiting or enhancing apoptosis in a cell, comprising:

(a) identifying an inhibitor or enhancer of apoptosis according to a method selected from the group consisting of claims 66-68, 70, 72, 76, and 80; and

(b) derivitizing the compound of (a) and optionally repeating at least one of steps (a) and (b),

to produce a compound that inhibits or enhances apoptosis.